THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

The Examiner has rejected pending claims 27-51 under 35 U.S.C. § 112 first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to convey to one skilled in the relevant art possession of the invention. Amendments have been made to clarify the design characteristics of the claimed antisense oligonucleotide (AO) which result in the function of treating cancers being achieved, i.e., complementarity of the AO to the recited strategic site encoded by the bcl-2 gene (SEQ ID NO:19). Complementarity of the AO to the various claimed strategic sites is supported by the specification at page 20. Applicants respectfully assert that the invention as presently claimed is fully described by the instant specification and as such, the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

The claimed methods and pharmaceutical compositions of the instant application relate to antisense oligonucleotides (AO) that by virtue of complementarity specifically target strategic accessible sites of the bcl-2 gene (SEQ ID NO 19). The claimed pharmaceutical compositions of the invention therefore have therapeutic and clinical utility for disorders relating to overexpression of the bcl-2 gene product, such as cancer and autoimmune disease. Applicants assert that the instant application provides the necessary written description for one skilled in the art to design and implement effective bcl-2 AO for therapeutic use as claimed without undue experimentation. Identification of additional sequences complementary to the claimed target sites within SEQ ID NO:19, choice of route of administration, formulation development, etc. are within the skill in the art and routine in the field once efficacious target sites are discovered, as discussed in more detail by Professor Finbarr E. Cotter, in the enclosed Declaration (the "Cotter Declaration"), whose cites to the published art (including his own publications), support Applicants' assertions. Applicants therefore request that the rejection of Claims 27-51 for lack of written description be withdrawn.

The claims allegedly lack written description for the term "hybridizing". For clarity, "hybridizing" has been replaced with the term "complementary to". The sequence of the bcl-2 gene is set forth in the specification and is well known in the art. One skilled in the art can readily determine what sequences are complementary to the claimed regions of the bcl-2 gene, and recognize that complementarity is the structural basis for the function of the AO in treating cancer.

The Examiner further contends that claims 43, 44 and 46 lack written description for a representative number of species of the claimed antisense to splice donor, splice acceptor and cap region of SEQ ID NO:19. Applicants respectfully remind the Examiner that when a skilled artisan understands the inventor to be in possession of the claimed invention, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. Applicants assert that although the specification has provided specific examples of antisense oligonucleotides for each of the strategic sites identified, using the general knowledge in the art relating to consensus sequences found in eukaryotic genes and the known sequence of the bcl-2 gene one skilled in the art would easily be able to identify other AO targeting splice acceptor and donor regions, the translation initiation site, the beginning of the open reading frame and the cap region. Applicants contend that one skilled in the art would be able to understand with ease the necessary structural features and limitations of the claimed invention when reading the specification in light of that well-known in the art at the time of filing. As such, claims 43, 44 and 46 are fully supported by the instant specification.

Claims 27-51 are rejected under 35 USC §112, first paragraph, for allegedly lacking enablement for the breadth of target regions claimed. The main focus of the Examiner's rejection appears to be that given the alleged unpredictability of the state of antisense technology, undue experimentation would be required for one skilled in the art to practice the claimed compositions and methods for those antisense oligonucleotides, other than SEQ ID NO:17. As evidenced by the Cotter Declaration submitted herewith, the instant specification fully enables one skilled in the art to practice the full scope of the claimed invention, *i.e.*, methods of treatment and pharmaceutical compositions directed to each of the claimed strategic sites, without undue experimentation, and as such the rejection should be withdrawn.

The Examiner incorrectly contends that claims 27-51 are not enabled for the administration of other antisense oligonucleotides to instant SEQ ID NO:19, or pharmaceutical compositions thereof, for the therapeutic functions claimed. Declarant establishes that the present invention provides examples of effective bcl-2 antisense oligonucleotides that are complementary to each of the claimed accessible strategic sites within the target RNA of bcl-2 and are therefore useful as human therapeutics in cancer and autoimmune diseases (*See*, the Cotter Declaration, paragraph 4). The specification clearly teaches the utility of the antisense oligonucleotides of the invention both *in vitro* and *in vivo*

cell-based assays. For example, the specification describes the inhibition of cell proliferation and the reduction of bcl-2 gene expression in lymphoid and leukemic cells using antisense oligonucleotides directed to each of the strategic sites of the invention (*See* Example 3, at page 22, line 10 to page 24, line 4). Antisense oligonucleotides directed to each of the strategic sites of the claimed invention are also demonstrated to mediate programmed cell death (*See* Example 12 at page 33, line 3 to page 35, line 7; *See* also, the Cotter Declaration, paragraph 3). Moreover, the specification also teaches an increase in the chemosensitivity of neoplastic cells to chemotherapeutic agents when treated with the antisense oligonucleotides directed to each of the strategic sites of the invention (*See* Example 18 at page 42, line 5 to page 57, line 11). Thus, the data presented in the specification clearly provides evidence that targeting each of the strategic sites of the bcl-2 gene has therapeutic efficacy as demonstrated by the cell based data presented therein.

The specification clearly provides that antisense oligonucleotides directed to each of the identified strategic sites of the bcl-2 gene have therapeutic utility, as evidenced by the cell based data provided therein (see Examples 12 and 18 of the present specification). Indeed, the predictive value of *in* vitro and cell-based assays is further evidenced by the successful application of SEQ ID No:17 in post-filing clinical trials for the treatment of cancer in humans (*See*, the Cotter Declaration at paragraph 4). Declarant confirms that these findings are consistent with the art accepted view that the inhibition of cell proliferation and the mediation of programmed cell death correlates with anti-cancer properties *See*, the Cotter Declaration, paragraph 6). As such, given the ability of each of the antisense oligonucleotides of the invention to inhibit cell proliferation and mediate programmed cell death as shown by the cell based data provided in the specification, each would be expected to have utility as a therapeutic for use in the claimed methods of the invention. Declarant also points out that no undue experimentation would be required to determine whether the claimed antisense oligonucleotides can indeed be used for the therapeutic functions claimed, *e.g.*, as cancer therapeutics (*See* the Cotter Declaration, paragraph 6).

As supported by the Cotter Declaration, Applicants assert that one skilled in the art would know how to identify AO within the scope of the claims, formulate pharmaceutical compositions and conduct suitable assays to determine their efficacy without undue experimentation. The true test of whether the experimentation required is undue, is whether it would require a level of ingenuity beyond that to be expected of one of ordinary skill in the art. *Fields v. Conover*, 443 F.2d 1386, 1390-1391, 170 USPQ 276, 279 (CCPA 1971). It would be considered routine experimentation to demonstrate that the anti-proliferative

response generated upon exposure of a host cell to an antisense oligonucleotide of the invention could confer anti-cancer properties in a human. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Intl Trade Comm 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

In further support, Applicants refer the Examiner's attention to the details of the Cotter Declaration and also to the examples in the art cited by Cotter, that assert the efficacy of each of the claimed bcl-2 antisense oligonucleotides of the invention. Dr. Cotter attests that the present specification "convincingly show(s) that specific binding of bcl-2 antisense oligonucleotide to the target bcl-2 gene reduces bcl-2 gene expression and results in the death of those cells" (*See*, the Cotter Declaration, paragraph 6). Furthermore, based upon published findings, the Cotter Declaration concludes that using the teaching in the present specification, "preclinical development, including *in vivo* animal studies, and then clinical development with clinical trials in the disease of interest, such as malignant disease, *e.g.*, lymphoma, is a matter of routine experimentation" (*See*, the Cotter Declaration, paragraph 6 citing Cotter, 1999, Biochemica et Biophysica Acta, 1489:97-106). Moreover, Dr. Cotter, citing to examples in the art that report the efficacy of the present invention, asserts that one skilled in the art, using routine experimentation, could simply apply the teachings of the present application to determine appropriate formulations and dosages of the bcl-2 antisense oligonucleotides (*See*, the Cotter Declaration, paragraph 8, citing Yang *et al.*, 1999, Proc. AACR, 40, Abstract 4814, and also paragraph 9). Such experimentation, while being time consuming and arduous, is routine and would not be considered undue (*See*, the Cotter Declaration, paragraph 8).

Applicants further refer the Examiner's attention to the Cotter Declaration, which cites specific examples in the art where the teachings of the present application have been successfully applied in more than one type of animal model (*See*, the Cotter Declaration, paragraph 9). Applicants point out, and the Cotter Declaration supports that one skilled in the art could, as a matter of routine experimentation, test the behavior of a bcl-2 antisense oligonucleotide in an animal model in order to determine pharmacokinetic and toxicity profiles. Moreover, the Cotter Declaration cites specific examples in the art where the teachings of the Reed application have been successfully applied in more that one type of animal model (See, *e.g.*, the Cotter Declaration, citing: 1) Cotter et al., 1994, Oncogene,

9(10): 3049-55; 2) Bosma et al., 1983, Nature. 301: 527-530; 3) McCune et al., 1988, Science, 241: 1632-1639; and 4) Cotter et al., 1996, Ann. Oncol. 7 Suppl. 3: 32). As such, the claims meet the requirements endorsed by the Federal Circuit and therefore are enabled for their inventive purposes.

The Examiner, relying upon references in the art cited in the present Office Action, further contends that the claims are not enabled due to the unpredictability in the art related to the subject technology. Furthermore, the Examiner contends that while the claims are considered enabled for the breadth of methods and pharmaceutical compositions that embrace the use of the antisense oligonucleotide of SEQ ID NO:17, the claims are not considered enabled for any other antisense oligonucleotide due to said unpredictability. Applicants point out that the instant invention is pioneering in the field of antisense based therapeutics as it solves numerous challenges that faced the state of the art as of the priority date of the instant application. As cited in Dr. Cotter's Declaration and also in his associated publications, a number of limitations were present in the field of antisense oligonucleotide based cancer therapy, such as specificities of the antisense oligonucleotides, susceptibility to degradation, limited cellular bioavailability, and non-specific effects (*See*, the Cotter Declaration, paragraph 7; and also Cotter, 2000, "Antisense Therapy for Malignancy" 338-348). However, as confirmed by the Cotter Declaration, these challenges have been overcome by the antisense oligonucleotides of the present invention (*See*, the Cotter Declaration, paragraph 7). Furthermore, Dr. Cotter, in his Declaration and associated publications also provides evidence that ordinary skill in the art has been used to overcome the challenges that face the researcher in the field of antisense oligonucleotide based therapeutics (*See*, the Cotter Declaration, paragraph 10, citing Cotter, F., 2000, "Antisense Therapy for Malignancy", 338-348; and Kuss *et al.*, 1999, Annals of Oncology, 10: 495-503; and Cotter *et al.*, 1999, Biochimica et Biophysica Acta 1489:97-106). In the cited examples, Dr. Cotter provides proof that all of the described antisense oligonucleotides currently in clinical trials were designed in accordance with the methodology set forth in the present application (*See*, the Cotter Declaration, paragraph 10). Indeed, the Cotter Declaration asserts and proves that the present invention has solved the problems cited by the Examiner as creating an unpredictability in the art and provides the information required by one of ordinary skill in the art to overcome the obstacles facing antisense oligonucleotide based bcl-2 therapeutics (*See*, the Cotter Declaration, paragraph 7).

Prior to the instant invention, antisense oligonucleotide based therapy was rarely successful, in part due to the failure in designing a sequence-specific antisense

oligonucleotide that targeted an appropriate site, *e.g.*, an accessible site, in the target gene, susceptibility to degradation, limited cellular bioavailability and non-specific effects. However, the inventors have overcome these difficulties by identifying target accessible sites within the target bcl-2 gene and by designing sequence-specific antisense oligonucleotide that target those sites. For example, the antisense oligonucleotides of the invention have a specific antisense effect as confirmed by the complete inability of the sense control oligonucleotides to affect cell growth (*See*, the Cotter Declaration, paragraph 7; and Example 3 of the present specification). In further support, Applicants point the Examiner's attention to the Cotter Declaration, where Dr. Cotter asserts that the specification of the instant invention clearly demonstrates the ability of bcl-2 antisense oligonucleotides to permeate the cell membrane of a eukaryotic cell so that a specific antisense effect is appreciated (*See*, the Cotter Declaration, paragraph 3 and paragraph 7). Also, Dr. Cotter asserts that the bioavailability of the antisense oligonucleotides of the present invention is demonstrated by their ability to permeate the cell membrane and effectively target the bcl-2 mRNA in its native state (*See*, the Cotter Declaration, paragraph 7; and Examples 3, 12 and 18 in the present specification). Applicants have also demonstrated the stability of the antisense oligonucleotides of the invention *in vivo* by virtue of their ability to traverse the cell membrane intact and successfully target bcl-2 mRNA (*See*, Cotter Declaration, paragraph 7; and Examples 3, 12 and 18 of the present specification). As such, Applicants have overcome the technical hurdles associated with antisense technology and have clearly provided a sufficiently enabling disclosure to allow one skilled in the art to practice the full scope of the claimed invention without undue experimentation.

Applicants respectfully request that the Examiner's rejection of claims 27 to 51 under 35 U.S.C. § 112, first paragraph, be withdrawn for the forgoing reasons. Applicants believe that each ground for rejection or objection has been overcome or obviated, and that all of the pending claims are in condition for allowance.

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Respectfully submitted,

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